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(54) USE OF TOREMIFENE FOR TREATING SLE

VERWENDUNG VON TOREMIFENE FÜR DIE BEHANDLUNG VON SLE

UTILISATION TOREMIFENE POUR TRAITER SLE

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Description

[Technical Field]

[0001] The present invention relates to use of toremifene for the preparation of a medicament for treating systemic lupus erythematodes, which is an autoimmune degenerative disease of kidneys.

[Background Art]

[0002] Immunosuppressants, nucleic acid antagonists, antimetabolites, etc., are used in the medicinal treatment of autoimmune diseases today. Anti-inflammatory agents, anticoagulants, etc., are also used in the symptomatic therapies of the diseases. The effects of these agents are, however, not yet sufficient.

[0003] It is known that the immunosuppressants have side effects of provoking diabetes, renal disorders, infectious diseases, etc. Also the use of the nucleic acid antagonist or antimetabolite is frequently accompanied by side effects such as hepatic disorders and medullary disorders. Thus the medicinal treatment of autoimmune diseases is so far very insufficient.

[0004] EP-A-0 415 623 discloses the use of toremifene or its metabolite N-demethyltoremifene or 4-hydroxytoremifene for the reversal of multidrug resistance of cancer cells to cytotoxic drugs in the treatment of cancer with at least one cytotoxic drug.

[0005] British Journal of Dermatology (1989) 121, 135 - 137 discloses the improvement of autoimmune progesterone dermatitis with the non-steroidal anti-oestrogen tamoxifen.

[0006] The treatment of autoimmune progesterone dermatitis with tamoxifen is also disclosed in Ann. Dermatol. Venerol. vol. 188, No. 8, 1991, pages 551-555.

[0007] J. Clin. Lab.Immunol. vol. 13, No. 1, 1984, pages 11-14 reports on the lack of improvement found after tamoxifen treatment of patients with systemic lupus erythematodes.

[0008] The effect of the anti-estrogen nafoxidine on NZB/W autoimmune disease is described in Arthritis and Rheumatism, vol 21, No. 4 (May 1978), page 414 - 417.

[0009] It has been demanded to develop a remedy for systemic lupus erythematodes which acts on the immune system and which has a function mechanism different from that of conventional drugs for the disease and less serious side effects.

[Disclosure of Invention]

[0010] After intensive investigations made for the purpose of finding the above-described remedy, the present inventors have found that toremifene has an excellent therapeutic effect on systemic lupus erythematodes and thus, based on this finding, completed the present invention.

[0011] The present invention relates to a use of toremifene or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating systemic erythematodes.

[Brief Description of Drawings]

[0012]

Fig. 1 shows survival times of animals (NZBxNZW F1 mice:B/W F1 mice) which accepted different doses of toremifene.

[Best Mode for Carrying Out the Invention]

[0013] Toremifene is a known compound (JP-B-4 19973). It is well-known that this compound has an anti-neoplastic effect (see Cancer Chemotherapy and Pharmacology, 17, 109-113 (1986) and the above-mentioned patent publication).

[0014] The pharmaceutically acceptable salts thereof include, for example, hydrochlorides, sulfates, citrates, tartrates and phosphates.

[0015] The medicament prepared according to the present invention is administered orally, parenterally or intravenously.

[0016] Usually, a pharmaceutically effective amount of the active ingredient is used in combination with a suitable medicinal carrier or other auxiliaries. The term "pharmaceutically effective amount" herein means an amount capable of exhibiting the intended pharmacological activity without causing unfavorable side effects. The accurate amount var-

ies in each case depending on various factors such as administration methods, individual natures of the patients and situations in which the patient accepts the remedy.

[0017] Dose of the active ingredient for adult is usually 10 to 1000 mg/day, preferably 20 to 500 mg/day, more preferably 30 to 300 mg/day.

[0018] The medicinal carrier or other auxiliaries generally usable in combination with the active ingredient according to the present invention may be any of solid and liquid ones and usually selected in consideration of an administration route. Examples of the solid carrier include lactose, sucrose, gelatin and agar, and those of the liquid carrier include water, syrup, peanut oil and olive oil. Other suitable carriers and auxiliaries known by those skilled in the art are also usable. The active ingredient according to the present invention can be combined with the carrier or other auxiliaries to form any of various acceptable preparations such as tablets, capsules, suppositories, liquid, emulsion and powder.

[0019] In the medicament prepared according to the present invention, the amount of the nonsteroidal anti-estrogen or the pharmaceutically acceptable salt thereof can widely vary depending on the preparation, etc. Usually, the amount is 0.01 ~ 100% by weight, preferably 0.1 ~ 70% by weight, and the balance contains the medicinal carrier or other auxiliaries.

[0020] MRL/Mp-lpr/lpr mice spontaneously develop a lethal glomerulonephritis, angitis, sialadenitis, polyarthritis, etc., concurrently with the deposition of an immune complex with age. Therefore, they are widely used as experimental models for human systemic lupus erythematodes, Sjögren's disease, rheumatoid arthritis and autoimmune angitis such as multiple arteritis.

[0021] The present invention will be explained referring to examples on suppression of lymphadenopathy glomerulonephritis, angitis, sialadenitis and arthritis of MRL/Mp-lpr/lpr mice with the nonsteroidal anti-estrogen compound toremifene according to the present invention.

Example 1

Treatment of spontaneous autoimmune diseases of MRL/Mp-lpr/lpr mice by administration of 2[4-(Z)-4-chloro-1,2-diphenyl-1-butenyl]phenoxy-N,N-dimethylethylamine citrate (toremifene citrate)

[0022] Eight-week old female MRL/Mp-lpr/lpr mice (Clea Japan, Inc.) were used in this examination. Toremifene citrate (JP-B-4 19973) was suspended in carboxymethylcellulose to prepare a 0.5% suspension. This compound (100 mg/kg) was orally administered to each mouse once a day for 13 weeks.

(A) Inhibition of swelling of spleen and lymph node of MRL/Mp-lpr/lpr mice with toremifene citrate

[0023] Repeated oral administration of 100 mg/kg of toremifene citrate once a day for 13 weeks inhibited the swelling of the spleen and lymph node of each mouse (see Table 1).

[0024] The spleen and lymph nodes of the MRL/Mp-lpr/lpr mice are seriously swollen with age due to the presence of the lymphoproliferation gene (lpr). The lpr codes for the Fas antigen in each mouse. However, in the MRL/Mp-lpr/lpr mice, an abnormality of the genes disturbs the expression of the Fas antigen. As a result, autoreactive T-cells are not subjected to negative selection through the Fas antigen in the thymus and appear in the peripheral tissues to cause the swelling of the lymphoid organs and autoimmune symptoms. The presence of the autoreactive T-cells was confirmed also in the autoimmune diseases of human beings, such as rheumatoid arthritis.

[0025] The results of this study indicated that the nonsteroidal anti-estrogen compounds such as toremifene citrate are capable of inhibiting the appearance of the autoreactive T-cells, thereby suppressing the swelling of spleen and lymph node to treat the autoimmune diseases.

Table 1: Effect of toremifene citrate[1] on swelling of spleen and lymph node MRL/Mp-lpr/lpr mice

Group	Number of animals	Spleen weight / Body weight [4]	Lymph node weight / Body weight [5]
Control [2]	11	2.34±0.74 [3]	6.77±1.70
Toremifene citrate treatment	12	1.38±1.06	3.11±1.43

1) Toremifene citrate (100 mg/kg) was orally administered to 8-week old mice once a day for 13 weeks.

2) Only 0.5% carboxymethylcellulose was given to the mice of the control group.

3) Standard deviation

4) Spleen weight/body weight $= \frac{\text{Weight of spleen}}{\text{Body weight of mouse}} \times 100$

5) Lymph node weight/body weight $= \frac{\text{Weight of lymph node}}{\text{Body weight of mouse}} \times 100$

(B) Suppression of renal disorder of MRL/Mp-lpr/lpr mouse with toremifene citrate

[0026] An autopsy was performed on the mice of the control group and the toremifene citrate treated group after the completion of the administration to examine their kidneys pathohistologically. The blood urea nitrogen (BUN) of the serum in each group was examined to confirm changes in the renal function. As shown in Table 2, toremifene citrate ameliorated the glomerulonephritis and healed the renal function in the MRL/Mp-lpr/lpr mice.

[0027] The glomerulonephritis of the MRL/Mp-lpr/lpr mice is caused by the deposition of immunocomplexes. Also in the case of the autoimmune diseases such as systemic lupus erythematodes (SLE) of human, the patients suffer from glomerulonephritis concurrent with the deposition of the immunocomplex. The results indicated that the nonsteroidal anti-estrogen compounds such as toremifene citrate are effective remedies for the degenerative diseases of the kidney, such as the SLE with renal syndrome and glomerulonephritis.

Table 2

Improvement of renal function and amelioration of glomerulonephritis of MRL/Mp-lpr/lpr mice with toremifene citrate			
Group	Number of animals	Glomerulonephritis [1]	BUN (mg/dl)[2]
Control	11	2.4 ± 0.7 [3]	43.1±23.9
Toremifene citrate treatment	12	1.2 ± 0.7	24.6±4.9

1) The kidney was fixed in 10% buffered formalin, and then paraffin sections thereof were prepared by an ordinary method to prepare HE and PAS stained specimens. The extent of the disorder of the renal glomeruli was scored and classified into the following groups:
0 (no disorder),
1 (slight disorder),
2 (medium disorder), and
3 (heavy disorder).
Twenty-five renal glomeruli were observed for each mouse and the average thereof was calculated.
2) The BUN was determined with a Fuji Dry Chem Analyzer.
3) Standard deviation.

Example 2

Comparison of survival time

[0028] NZB x NZW mice (B/W F1 mice) were used as a pathological model of autoimmune diseases (systemic lupus erythematodes). Effect of toremifene citrate on the survival time of the animals was investigated.

Experimental animals:

[0029] F1-hybrids of NZB (female) and NZW (male) mice (B/W F1 mice): Imported from Bomholtgaard, Denmark at the age of five weeks.

Test Groups and doses:

[0030]

Control (male):	administration polyethyleneglycol (peg) 3 times a week per os
Control (female):	administration peg 3 times a week per os
Toremifene citrate 30 mg/kg/day:	administration 70 mg/kg in polyethylene glycol solution 3 times a week per os to female NZB x NZW F1 mice
Toremifene citrate 3 mg/kg/day:	administration 7 mg/kg in polyethylene glycol solution 3 times a week per os to female NZB x NZW F1 mice

[0031] The survival time of the animals in different test groups is presented in Fig. 1. All but two female control animals have died during the almost two years' follow-up time. Fifty percents of the animals in this group died before/at the age of 40 weeks, and 20% (4/20) were alive after one year.

[0032] In the male control group, five animals died during the first 24 weeks (not shown in Fig. 1) due to aggressive behaviour and thereby acquired infection. These five were excluded from the results. Forty-seven percents of the male control mice are still alive after almost two years' time.

[0033] In both toremifene treatment groups the life span of the animals has lengthened clearly when compared to the female control animals. In the 3 mg/kg toremifene treatment group only one (1/20) animal had died at/before the age of 40 weeks and three (3/20) animals in the 30 mg/kg toremifene group.

[0034] After one year 80% and 85% of the animals were alive in the 3 mg/kg and 30 mg/kg toremifene treated groups, respectively, which is nearer the percentage of the male control animals (≈ 90%) than that of the female control group (20%).

[0035] Moreover, 25% (5/20) and 10% (2/20) of the animals are still alive after almost two years' time in the lower and higher toremifene dosage group, respectively.

[0036] The follow-up data of 60 female and 15 male F1-hybrids of NZB x NZW F1 mice (B/W F1 mice) show that

toremifene treatment has clearly extended the life span of female mice.

Example 3

[0037] Examples of preparations comprising the toremifene or the pharmacologically acceptable salt thereof as active ingredient will be given below, which by no means limit the preparations of the present invention.

Preparation Example 1

Formulation of prepared 200 mg tablet.

[0038]

Toremifene citrate	20 mg
Starch	85 mg
Lactose	90 mg
Magnesium stearate	5 mg

Claims

1. Use of toremifene or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating systemic Lupus erythematodes.

Patentansprüche

1. Verwendung von Toremifen oder eines pharmazeutisch verträglichen Salzes davon für die Herstellung eines Medikamentes zur Behandlung des systemischen Lupus erythemathodes.

Revendications

1. Utilisation de torémifène ou d'un sel pharmacologiquement acceptable de celui-ci pour la préparation d'un médicament pour traiter le lupus érythémateux aigu disséminé.

FIG. 1